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Potential employment of transcranial magnetic stimulation as a beneficial intervention in children with amblyopia: a brief overview

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ABSTRACT

Amblyopia is an early functional imbalance between each eye and the brain that may result in visual cortex inhibition. Current conservative treatments involve altering the input from the 'good eye', for example, using patching or biochemical penalization. Direct brain stimulation to the amblyopic cortex might improve the condition. This paper aimed to systematically review the published scientific literature regarding the use of transcranial magnetic stimulation (TMS) as a potential method for treatment in the amblyopic visual cortex. This study was a systematic review of the published scientific literature related to the TMS for the treatment of amblyopia that was performed using "TMS, amblyopia" as keywords. However, only three research papers were found and included in the literature review. A study showed that repetitive TMS of the visual cortex can temporarily improve contrast sensitivity in the amblyopic visual cortex. Another study used continuous theta burst stimulation (cTBS) delivered to the visual cortex while patients viewed a high contrast stimulus with their non-amblyopic eye. It was found that daily theta burst TMS stimulation improved amblyopic eye contrast sensitivity in five adult volunteers. The TMS also increased median visual acuity in the patient with amblyopia after stimulation with no significant changes in the placebo group. Protocol employing repetitive administration of TMS might result in beneficial effects in amblyopia treatment. TMS works in brain dynamics and experience-dependent plasticity, all of which could be important in investigating and treating amblyopia.

ABSTRAK

Ambliopia adalah ketidakseimbangan fungsi antara kedua mata dengan otak yang dapat menyebabkan hambatan korteks visual. Terapi konservatif saat ini melibatkan perubahan input dari 'mata yang baik' dengan menggunakan patching atau obat-obatan. Stimulasi otak langsung ke korteks ambliopik dapat mengatasi kondisi hambatan pada korteks visual tersebut. Makalah ini bertujuan untuk meninjau secara sistematis mengenai penggunaan stimulasi magnetik transkranial (Transcranial Magnetic Stimulation/TMS) sebagai metode potensial untuk pengobatan di korteks visual ambliopik. Tinjauan sistematis literatur ilmiah ini adalah mengenai penggunaan TMS untuk pengobatan ambliopia dengan menggunakan "TMS, amblyopia" sebagai kata kunci. Hanya tiga hasil penelitian yang ditemukan dan dapat digunakan dalam tinjauan literatur. Sebuah penelitian menunjukkan bahwa TMS pada korteks visual berulang dapat memperbaiki sensitivitas kontras sementara pada korteks visual ambliopik. Studi lain menggunakan stimulasi theta burst yang diberikan pada korteks visual saat pasien melihat stimulus kontras tinggi dengan mata non-ambliopik. Ditemukan bahwa stimulasi theta burst TMS secara teratur meningkatkan sensitivitas kontras mata ambliopik pada lima relawan dewasa. TMS juga meningkatkan median ketajaman visual pada pasien dengan ambliopia setelah stimulasi tanpa perubahan signifikan pada kelompok plasebo. Protokol pemberian TMS berulang bermanfaat dalam pengobatan ambliopia. TMS bekerja dalam dinamika otak dan experience-dependent plasticity.

Keywords:
amblyopia;
transcranial magnetic stimulation;
pediatric ophthalmology;
visual cortex;
refractive correction;

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INTRODUCTION

Early visual deprivation, for instance, as a result of cataracts or due to refractive error, causes a reduction in the early sensory input that plays an important role in tuning the visual cortex.[1] Amblyopia is the most common cause of monocular visual loss in children and young adults, occurring at a rate between 1 and 3.5% in developed countries.[2] This condition is the result of reduced processing of the neural signals related to visual information from the amblyopic eye during visual development and is clinically defined as a two-line difference (in Snellen's chart) of best-corrected visual acuity between the eyes.[3] Several problems can commonly lead to amblyopia, either alone (e.g. a need for glasses as a consequence of refractive error, strabismus) or in combination.[2]

Conservative approaches, such as refractive correction or optical penalization using either pharmacological or physical methods, are often used in current treatments of amblyopia. The latter may use an eye patch or surgical interventions; for example, cataract extraction needs to be performed. In terms of examining the effectiveness of physical interventions, a study of patients with both moderate and severe bilateral amblyopia found excellent improvement in visual acuity with the use of glasses alone.[4] Another study investigating moderate amblyopia reported that, when an eye patch was used as treatment, a greater number of hours of patching did not produce either a clinically or statistically significant effect when used for six months.[5] It was reported, however, a faster rate of initial rate of improvement in a group patched for 6 hours daily compared with a group patched for two hours. When the use of atropine on weekends in severe amblyopia was assessed, a similar potential for effective improvement in visual acuity was observed.[6,7] Patients with full glasses correction and weekend atropine administration showed an average of 4.5 lines of improvement after 18 weeks. A study showed that visual acuity was significantly better in those receiving citicoline and patching than in the group receiving only patching.[8]

Transcranial magnetic stimulation (TMS) is a tool that can make it possible to evaluate the need for the role of the brain region in cognitive function. This primarily means that it can provide an alternative to lesion-based investigations, which means that more tasks and functions can be investigated and have good spatial characteristics and excellent resolution in the temporal domain.[9,10] Since its development as a viable experimental tool, researchers have used TMS to investigate numerous functions, including (but not limited to) investigating parietal neglect, studies of the perception of visual motion, perceptual priming, the role of synchronized cortical discharge, conscious visual awareness, visual search and study of interactions between cortical areas.[11-20]

While treatment regarding refractive correction is only effective in treating the refractive cause of amblyopia, suppression using patching and atropine are not beneficial in terms of restoration of binocular function. If it is reasonable, one of the ideal objectives when treating amblyopia is an improvement of vision by eliminating the inhibitory signal from the normal eye and allowing normal development related to the amblyopic eye to occur. Therefore, a combination of stimulation of the suppressed neural system in combination with reduction of the suppression from the other eye may be necessary as first steps in any binocular therapy. This paper aimed to systematically review the published scientific literature regarding the use of TMS as a potential method for treatment in the amblyopic visual cortex before conducting TMS in amblyopia patients.

MATERIALS AND METHODS

Literature research

A systematic literature search was undertaken during the period of October 2019. Search strategies were performed to identify literature pertaining to amblyopia, amblyopia treatment, children, and TMS terms. No date or language restrictions were applied. A total of 236 articles were identified through the database searches. Letters, reviews, and editorials describing other studies reporting TMS application in amblyopia were excluded. Only three articles were eligible for analysis after identification through the database searches.

Data extraction and synthesis

The papers examined were in terms of instruments, patient selection, and TMS protocol.

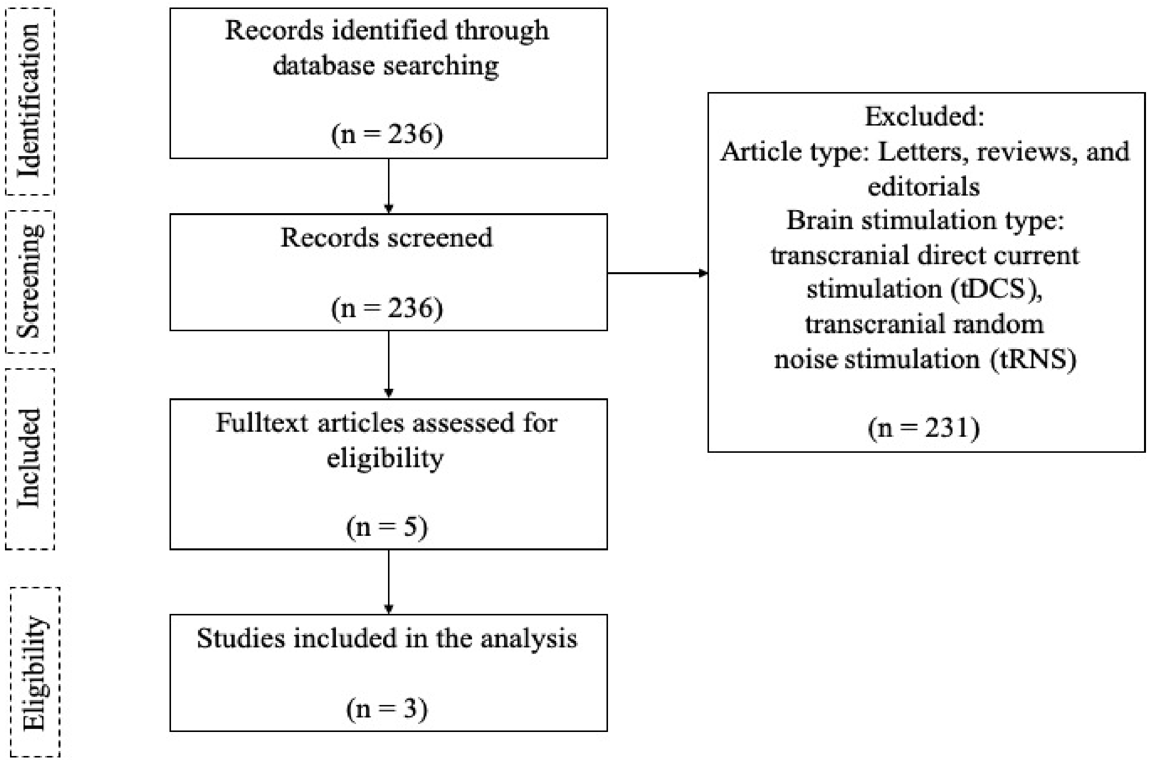

FIGURE 1. PRISMA flow diagram of study identification

RESULTS

The use of TMS in amblyopia treatment is relatively new and has not been developed before. There have been only a few studies investigating the effects of TMS in treating amblyopia. One study showed that repetitive TMS of the visual cortex can temporarily improve contrast sensitivity in the amblyopic visual cortex.[21] In this study, 7 of 9 patients responded to 1 Hz TMS stimulation at one or both post-TMS time points investigated. When 10 Hz stimulation was used, all six participants tested showed improved contrast sensitivity at both time points. Importantly, both participants who did not respond to 1 Hz stimulation did show a response to 10 Hz stimulation.[21] Another study used continuous theta-burst stimulation (cTBS) delivered to the visual cortex while patients viewed a high contrast stimulus with their non-amblyopic eye. It was found that daily theta-burst TMS stimulation improved amblyopic eye contrast sensitivity in five adult volunteers.[22] cTBS was effective in improving amblyopic eye contrast sensitivity for high spatial frequencies, with an improvement across sessions. Asymptotic levels of performance were attained after just two daily sessions of stimulation. Notably, such improvements were stable up to 78 days after stimulation.[22]

A current study included eight participants (six women and two men) with amblyopia with a median visual acuity after stimulation of 0.18 (0.05–0.34) (before stimulation: 0.28; range: 0.14–0.49) and no significant changes in visual acuity for the placebo group.[23]

TABLE 1. Summary of the previous research

Study	Protocol	Design	Stimulation area	Control area	Stimulus	Parameter	Effect
Thompson *et al.*[21]	1 Hz repetitive TMS at visual cortex	Patient-control Psychophysics design	Visual cortex	Motor cortex	Contrast-sensitivity Gabor patch grating,	% contrast	2.5% contrast increment
Clavagnier *et al.*[22]	Continuous theta-burst TMS	Experimental of 5 amblyopic patients	Visual cortex, MRI located	-	Contrast-sensitivity Gabor patch grating,	Log-contrast	0.5 log-contrast increment
Tuna *et al.*[23]	Continuous theta-burst TMS	Patient-control design	Visual cortex, phosphene located	-	No-stimulus, phosphene induce stimulation	Stereoacuity, suppressive imbalance	1.4 decrease of suppressive imbalance

Note: TMS: transcranial magnetic stimulation; MRI: magnetic resonance imaging

DISCUSSION

There were very few studies that involved the application of TMS in amblyopia patients; therefore, it might provide a wide opportunity for researchers in this field to develop a more standard TMS protocol and safety procedure to be applied to amblyopia patients. From the results of this study, the application of TMS to the amblyopic visual cortex has been found to improve contrast sensitivity,[21] albeit temporarily. Either repeated TMS or theta burst stimulation has been shown to modulate abnormal interhemispheric patterns of suppression inhibition within the human cortex, which leads to the suggestion that these techniques may be useful in reducing pathological suppression. Delivery of repetitive TMS effectively causes externally induced changes in neuronal spiking, meaning that cortical activity can be altered in a manner that is both spatially and temporally precise. Under normal conditions, TMS could excite a functional inhibitory circuitry. An example of this is the circuit between the prefrontal cortex and the superior colliculus involved in the control of eye movements.[24]

Brain plasticity determines the effectiveness of TMS in exciting the suppressed brain area in amblyopic patients. It is assumed that the amblyopic eye is capable of functioning well since a surprising level of plasticity after age 6 has been shown in individuals with amblyopia[1]. The effects of excitatory stimulation also tend to be more pronounced for neurons with a recent history of suppression, and it also seems that the effects of inhibitory stimulation may be more pronounced for recently activated neurons.[25-27] It has been shown that TMS delivered to the visual cortex can result in modulation of a range of measures, including contrast sensitivity, motion perception, visual evoked potentials and phosphene thresholds, the latter being the strength of a single pulse of TMS delivered to the occipital lobe needed to induce the percept of a phosphene and often used as a measure of visual cortex excitability.[9] TMS has also been suggested to be potentially beneficial in terms of resulting in therapeutic effects in patients, with promotion of exogenous plasticity that may have a "potentiating effect" when it occurs in combination with endogenous mechanisms.[28]

Importantly, there is currently no evidence of undesirable short-term or long-term effects related to the use of TMS, and it is commonly described as a "relatively painless method" for noninvasive brain stimulation.[11,29] However, this certainly does not mean safety should not be a major factor that is considered when using TMS in humans, and even more so when considering use in children. Frye *et al.*[29] reviewed studies specifically in terms of considering the diagnostic and therapeutic use of TMS in child populations. They looked at 84 studies involving the use of TMS in children, with a total of more than 800 normal children and 300 neurologically abnormal children.[29] Fifteen of the studies evaluated mentioned no occurrences of any side effects, one mentioned that there was an adverse effect,[29] and another study mentioned that stimulation had resulted in a transient dullness on the subject's left upper limb.[30,31] One possible source of concern relates to the smaller size (circumference) of children's heads compared to adults. However, despite this smaller head circumference, the actual brain volume does not vary much from six years of age.[32] In addition, open fontanels in young children younger than 18 months indicate the need for special care related to coil placement to prevent mechanical injury. The potential effects of an open fontanel on the distribution-induced electrical field should also be considered.[33]

An additional issue for consideration, and of significant relevance to the quality of the data in a study, is that TMS delivery can cause significant sensory sensations that might result in nonspecific interference with task performance. These include a loud clicking sound when the stimulator is discharged, as well as potential for stimulation of both cranial nerves and direct activation of facial and neck muscles.[29] Despite these issues, the previous study found no evidence of hearing loss in humans due to the noise associated with TMS, with the risk of hearing loss from the sounds that result from magnetic stimulation that seems to be small.[34] These sounds can be minimized, with benefits for both data collection and, importantly, minimization of any potential health effects, by use of hearing protection such as earplugs or earmuffs when TMS is delivered. However, there are no data on the risks of hearing damage in children less than two years of age, and guidelines suggest special care must be taken to protect hearing, such as the use of specialized hearing protection when applying TMS to children.[33]

However, it is currently not possible to identify the exact mechanisms that result in rTMS-based improvement in visual functions. It has been suggested that TMS may promote equality in neural excitability between the two eyes. This may act to return a neural system to equilibrium in amblyopics.[21] Future studies have the potential to assess this more specifically.

CONCLUSION

In conclusion, TMS has the potential to improve visual acuity and contrast sensitivity in amblyopia patients.

However, there is a lack of standardized protocols and outcome parameters. TMS is generally safe for use in human subjects (when employed in a suitable manner and following appropriate guidelines) and has been widely employed in numerous experiments to test hypotheses related to a range of cognitive processes as well as to offer insight into both local and global brain network organization, brain dynamics and experience-dependent plasticity, all of which could be important in investigating and treating amblyopia. Specifically, data collected so far seem to suggest that a protocol employing repetitive administration of TMS may result in beneficial effects that persist beyond the period of stimulation.

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